REMARKS

This Amendment and Response is submitted in response to the Office Action, mailed January 3, 2005. A check for $5220 for the fee for a three-month extension of time ($1020) and the fee for excess claims ($1400 for seven additional independent claims and $2800 for 56 additional dependent claims) accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 2-16, 18-28 and 30-47 are pending. Claims 1, 17 and 29 are canceled herein without prejudice or disclaimer. Claims 2-6, 8, 12, 13, 18-22, 24, 28, 33-35 and 41 are amended to change their dependency. Claims 9-11 and 25-27 are amended herein to be independent claims, incorporating all of the limitations of the base claim. Claims 28, 30, 33-35 and 43 are amended to more distinctly claim the subject matter by including the wording of the preamble into the body of the claim. Claims 28, 30, 33-35 and 43 are also amended to correct minor typographical errors. Claim 41 is amended to recite "hormone-dependent cancer." Basis for the amendment amended can be found throughout the specification (for example, see page 22, line 9-21). Claim 43 is amended to more distinctly claim the subject matter. Basis for the amendment can be found throughout the specification (for example, see page 34, lines 5-10). Claims 44-47 have been added. Basis for claims 44-46 can be found in original claim 1 and basis for claim 47 can be found in original claim 17 and throughout the specification (e.g., page 11, line 9, through page 21 line 1). Therefore, no new matter has been added.

I. REJECTION OF CLAIMS 1, 14, 17 AND 28-43 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1, 14, 17 and 28-43 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to describe the claimed subject matter in such a way as to enable one skilled in the art to make and use the claimed subject matter. The Examiner states that "the instant compounds are agonist at progesterone receptor as shown data in tables 1 and 2 on pages 67-68" (see Office Action, page 2) and that "based on this data, the instant compounds will have utility in treating disease conditions where progesterone receptor agonists are well known

in the prior art to have therapeutic effect (see Office Action, page 3). The Examiner, however, alleges that there is no teaching in the specification or the prior art showing therapeutic effect of progesterone receptor agonists, that there are no working examples showing efficacy of the instant compounds in known animal models of any disease condition where progesterone receptor agonist activity is implicated, and that it would require undue experimentation to demonstrate efficacy of the claimed compounds in known animal models of all disease conditions where progesterone receptor agonists activity is implicated in their etiology.

This rejection is respectfully traversed.

RELEVANT LAW

The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is whether it would require undue experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The starting point in an evaluation of whether the enablement requirement is satisfied is an analysis of each claim to determine its scope. The focus of the inquiry is whether everything within the scope of the claim is enabled. As concerns the breadth of a claim relevant to enablement, the only concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Once the scope of the claims is addressed, a determination must be made as to whether one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

It is incumbent upon the Examiner to first establish a *prima facie* case of non-enablement. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369-70 (CCPA 1971). The requirements of 35 USC §112, first paragraph, can be fulfilled by the use

of illustrative examples or by broad terminology. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973):

> ... we do not regard section 112, first paragraph, as requiring a specific example of everything within the scope of a broad claim ... What the Patent Office is here apparently attempting is to limit all claims to the specific examples, not withstanding the disclosure of a broader invention. This it may not do.

In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960) :

> It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it.

This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." *In re Marzocchi et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

The law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention. See *Vivid Technologies, Inc. v. American Science and Engineering, Inc.*, 200 F.3d 795, 804, 53 USPQ2d 1289, 1295 (Fed. Cir. 1999) ("patents are written by and for skilled artisans"). To hold otherwise would require every patent document to include a technical treatise for the unskilled reader. Although an accommodation to the "common experience" of lay persons may be feasible, it is an unnecessary burden for inventors and has long been rejected as a requirement of patent disclosures. See *Atmel Corp.*, 198 F.3d at 1382, 53 USPQ2d at 1230 (Fed. Cir. 1999) ("The specification would be of enormous and unnecessary length if one had to literally reinvent and describe the wheel."); *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983) ("Patents are written to enable those skilled in the art to practice the invention, not the public.")

The test of enablement is whether one skilled in the art can make and use what is claimed based upon the disclosure in the application and information known to those of skill in the art without undue experimentation. *United States v. Telectronics, Inc.*,

8 USPQ2d 1217 (Fed. Cir. 1988). A certain amount of experimentation is permissible as long as it is not undue. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. A patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent, Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987).

Applicant respectfully submits that the rejection as directed to claims 1, 17 and 29 is moot in light of the cancellation of these claims herein without prejudice or disclaimer. Claims 44-46 are directed to subject matter claimed in original claim 1 and claims 47-49 are directed to subject matter claimed in original claim 17. Thus, Applicant traverses the rejection below as though applied to added claims 44-49.

ANALYSIS

Application of the Factors Enumerated in *In re Wands*

As discussed in detailed below, a consideration of the factors enumerated in *In re Wands* demonstrates that the application, in conjunction with what was known to one of skill in the art, teaches how to make and use the subject matter as claimed in pending claims 14, 28 and 30-49 without undue experimentation.

A. Breadth of the Claims

Claim 1 is cancelled herein. Added claims 44-46 are directed to compounds of Formula I as defined in the claims.

Claim 14 is directed to compounds of Formula II as defined in the claims.

Claim 17 is cancelled herein. Claim 47 is directed to pharmaceutical compositions that include a compound of any one of claims 44-46.

Claim 28 is directed to a method of treating an individual having a condition mediated by a progesterone receptor that includes administering a compound of Formula I as defined in any one of claims 44, 45 or 46 or of Formula II as defined in claims 12 or 14. Claims 31 and 32 depend from claim 28 and are directed to embodiments thereof.

Claim 30 is directed to a method of treating an individual having a condition mediated by a progesterone receptor that includes administering a compound of Formula II as defined in the claim.

Claim 33 is directed to a method of modulating fertility of an individual that includes administering a compound of Formula I, as defined in any one of claims 44-46, or Formula II, as defined in claims 12 or 14.

Claim 34 is directed to a method of providing contraception to an individual that includes administering a compound of Formula I as defined in any one of claims 44-46, or of Formula II as defined in claims 12 or 14.

Claim 35 is directed to a method of modulating a progesterone receptor in an individual that includes administering a compound of Formula I as defined in any one of claims 44-46, or of Formula II as defined in claims 12 or 14. Claims 36-40 depend from claim 35 and are directed to embodiments thereof.

Claim 41 is directed to a method of treating hormone-dependent cancer that includes administering a compound of Formula I as defined in any one of claims 44-46, or of Formula II as defined in claims 12 or 14. Claim 42 depends from claim 41 and is directed to an embodiment thereof.

Claim 43 is directed to a method of determining the presence of a progesterone receptor in a cell or cell extract that includes contacting the cell or extract with a labeled compound of Formula I as defined in any one of claims 44-46, or of Formula II as defined in claims 12 or 14.

The compounds of Formula I and II as defined in the specification and as claimed are non-steroidal compounds that are progesterone receptor modulators and encompass agonists, partial agonists and antagonists (see page 2, lines 15-19). The exemplified and specifically claimed compounds demonstrate progesterone receptor agonist activity (e.g., Compounds 24, 25, 27, 28, 34, 35, 38, 41, 42, 44, 45 and 71) and antagonist activity (e.g., Compounds 37, 64 and 65 (see Table 1 on page 67). The claimed compounds can be used in pharmaceutical compositions. The compounds also can be used in methods of treating an individual having a condition mediated by a progesterone receptor, and in methods of determining the presence of a progesterone receptor in a cell or cell extract.

Applicant respectfully submits that the breadth of the claims is commensurate with the scope of the enabling disclosure provided in the specification. Using what is disclosed in the specification and known in the art at the effective time of filing the instant application, one of skill in the art can make and use any or all of the claimed compounds and compositions and methods of using the compounds or compositions.

B. Teachings of the Specification

1. Therapeutic Effect of PR Agonists

The Examiner alleges that there is no teaching in the specification or in the prior art references showing therapeutic effect of progesterone receptor agonists. Applicant respectfully disagrees. The specification teaches that progesterone receptor agonists, such as synthetic progestins, can be used as female birth control agents (see page 1, lines 19-22). The specification also teaches that progesterone receptor modulator compounds, which include agonists and antagonists, areuseful for female replacement therapy and as modulators of fertility, and for the treatment of other disorders. For example, see page 22, lines 9-21, which recites:

> PR modulator compounds of the present invention may be particularly useful for female hormone replacement therapy and as modulators of fertility (*e.g.*, as contraceptives, contragestational agents or abortifacients, *in vitro* fertilization, pregnancy maintenance), either alone or in conjunction with one or more estrogen modulators. PR modulator compounds of this invention also may be used in the treatment of dysfunctional uterin bleeding, dysmenorrhea, endometriosis, leiomyomas (uterine fibroids), hot flushes, mood disorders, and meningiomas. PR modulator compounds of this invention also may be used in the treatment of various hormone-dependent cancers, including, without limitation, cancers of ovaries, breast, endometrium and prostate. PR modulator compounds of this invention can also be used in treatment of female osteoporosis, either alone or in combinatyion with one or more estrogen receptor modulators.

Thus, the specification teaches that progesterone receptor agonists have therapeutic effect, such as for female birth control agents.

2. Prodrugs

The Examiner states that "the efficacy of a prodrug following *in vivo* administration depends upon release of parent compound to its target *in vivo*. A prodrug of any compound does not necessarily mean that the parent compound will be released *in vivo* since it is influenced by various factors, such as absorption,

metabolism, degradation by esterases, etc." The Examiner contends that "there is not even a single example present in the specification of any prodrug."

Applicant respectfully submits that the relevant standard is that a patent application satisfies the requirements of 35 U.S.C. § 112, first paragraph, as long as it provides sufficient disclosure, either through illustrative examples or terminology, to teach those of skill in the art how to make and use the claimed subject matter without undue experimentation. Applicant respectfully submits that the art at the time of filing was replete with guidance for preparing and using prodrugs. See e.g., Richard B. Silverman, *The Organic Chemistry of Drug Design and Drug Action*, Academic Press, Inc., (1992); Chapter 8: "Prodrugs and Drug Delivery Systems," pp 352-401 (copy enclosed). As discussed above, a patent application need not teach, and preferably omits, what is well known in the art. In view of the prior art, one of ordinary skill in the art could easily prepare prodrugs from any of the recited compounds of the claims.

Applicant also respectfully submits that the requirements of 35 U.S.C. §112, first paragraph, do not require a specific example of everything within the scope of the claims. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973):

> ...we do not regard section 112, first paragraph, as requiring a specific example of everything within the scope of a broad claim . . . What the Patent Office is here apparently attempting is to limit all claims to the specific examples, not withstanding the disclosure of a broader invention. This it may not do.

In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960) :

> It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it.

Hence there is no requirement for the applicant to exemplify or even provide an example of everything within the scope of the claims. Thus, the requirements of 35 U.S.C. §112, first paragraph, do not require a specific example of a prodrug.

C. State of the Prior Art

The Examiner alleges that there is no teaching in the prior art references showing therapeutic effect of progesterone receptor agonists. Applicant respectfully disagrees. Applicant respectfully submits that at the time of filing the application,

progesterone receptor agonists were known and used as therapeutic agents. For example, Bamberger *et al.* teaches using the PR agonist medroxyprogesterone acetate (MPA) for the treatment of inflammatory and autoimmune states (J Clin Endocrinol Metab 84: 4055-4061 (1999). Otsuki *et al.* teaches that progesterone and the synthetic progesterone receptor agonist R5020 inhibit tumor necrosis factor-α-activated VCAM-1 expression in vascular endothelial cells, and adding PR agonists to estrogen therapies to eliminiate the increased risk of endometrial cancer (Arterioscler Thromb Vasc Biol 21: 243-248 (2001). Zhi *et al.* teaches that progestins are used to treat several gynecological disorders, including dysmenorrheal, endometriosis, and dysfunctional uterine bleeding caused by hormonal deficiency or imbalance (J. Med. Chem. 41: 291-302 (1998)). Hence, progesterone receptor agonists are known in the art to have therapeutic effect.

In addition, the regulation of intracellular progesterone receptor concentration was known to play an important role in the physiology of the menstural cycle and in various diseases of the female genital tract (e.g., see Savouret *et al.*, J Biol Chem 269(46): 28955-28962 (1994)). Clarke *et al.* has shown that retinoic acid decreases the transcription of the progesterone receptor gene in T-47D human breast cancer cells, and that retinoic acid is capable of modulating sensitivity to progestins in human breast cancer cells (J Bio Chem 265(21): 12694-12700 (1990)). The inhibition of progesterone action in women using progesterone receptor modulators is used to prevent conception at a variety of stages (for example, see Giannoukos *et al.*, Molecular Endocrinology 15(2): 255-270 (2001)). In addition, antiprogestins are known in the art to provide safe effective means of medical abortion and in the treatment of patients with cancer, Cushing's syndrome, gynecologic disorders and for contraception (for example, see Spitz *et al.*, New Englan J Med 329: 404-412 (1993)). Copies of these articles are supplied herewith. Thus, use of progesterone receptor modulators, such as agonists or antagonists, as therapeutic agents was known to those skilled in the medical arts. There is a clear showing in the art that compounds that are active as progesterone receptor modulators, including progesterone receptor agonists and antagonists, are effective in the treatment of many specific disease conditions.

D. Level of Skill in the Art

The level of skill in the art of chemical synthesis and in the medical arts is high. This is evidenced by the art in this area, which is authored primarily by those with Ph.D. and M.D. degrees and is intended for an audience of similarly highly skilled individuals, primarily in the fields of biochemical, pharmaceutical, or medical arts. The numerous articles and patents made of record in this application, authored and reviewed by those known and of skill in the art further evidence the high level of skill in this art. The skill of those in these arts, together with the instant specification, including cited and incorporated references, allows the skilled artisan to make any and all of the claimed compounds. Therefore, the amount of disclosure required to meet the enablement requirement is minimal.

E. Knowledge of those of skill in the art

At the effective time of filing the application and before, those of skill in the art were very familiar with synthetic organic chemistry and medical chemistry. This is evidenced, for example, in the application and in literature made of record in the Information Disclosure Statements submitted. As discussed above, at the time of filing the instant application, the art was replete with references describing progesterone receptor agonists and their involvement in various diseases and conditions (for example, see Zhi *et al.*, J. Med. Chem. 41: 291-302 (1998)).

F. Predictability of the Art

The art of chemical synthesis is predictable and is dictated by recognized chemical reactions and constraints. The medical arts are also predictable, in that various assays and models that mimic an *in vivo* system in the laboratory were available and known to the skilled artisan at the time of filing of the application. For example, see U.S. Pat. No. 5,071,773 to Evans *et al.* (1991), which teaches a bioassay for evaluating whether compounds are functional ligands for receptor proteins. Such assays are routine in the medical arts. The specification directs one skilled in the art to references that describe a co-transfection assay and a receptor binding assay (for example, see pages 28, lines 3-17, directing the skilled artisan to Pathirana *et al.*, Mol. Pharma 47: 630-635 (1995)). References that establish links between the progesterone receptor and known disease states are known in the art (for example, Spitz *et al.*, New England J Med 329: 404-412 (1993)).

G. Working Examples

The Examiner alleges that the specification provides no working examples showing efficacy of the instant compounds in known animal models of any disease conditions where progesterone receptor agonist activity is implicated in their etiology. The Examiner further alleges that testing the "several hundreds of thousands" of claimed compounds to demonstrate efficacy in animal models would be undue experimentation.

1. Testing of the Compounds in Animal Models

Applicant is not aware of any requirement under current U.S. patent law specifying particular minimum levels of optimization and certified efficacy such that lack of enablement under 35 U.S.C. § 112, first paragraph, is not a consideration. There is no requirement that the utility of a pharmacologically active substance be proven by *in vivo* testing. *In re Isaacs*, 146 USPQ 193, 195 (CCPA 1965). *In vitro* tests can raise the presumption of *in vivo* utility of the claimed compounds. Applicant respectfully submits that evidence does not have to be in the form of data from an art-recognized animal model for the particular disease or disease condition to which the asserted utility relates (see MPEP 2107.03(III)).

The relevant standard is that a patent application satisfies the requirements of 35 U.S.C. § 112, first paragraph, as long as it provides sufficient disclosure, either through illustrative examples or terminology, to teach those of skill in the art how to make and use the claimed subject matter without undue experimentation. The specification directs one skilled in the art to references that describe a co-transfection assay and a receptor binding assay (for example, see pages 28, lines 3-17, directing the skilled artisan to Pathirana *et al.*, Mol. Pharma 47: 630-635 (1995)). Modulating activity in a co-transfection assay has been shown to correlate with *in vivo* modulating activity, and therefore such assays are predictive of *in vivo* activity (e.g., see Berger *et al.*, J Steroid Biochem Mol Biol 41: 773 (1992)). One of skill in the art would recognize that the assays described in the references and in the specification are useful in assessing certain compounds including those presently claimed in the treatment of disease conditions where a progesterone receptor has been implicated. As discussed above, a number of diseases are recognized to be sensitive to progesterones and to respond to progesterone receptor modulation therapy, including administering

compounds that are progesterone receptor agonists or progesterone receptor antagonists. Thus, compounds that demonstrate PR agonist or antagonist activity in bioassays, such as co-transfection assays and binding assays, are candidates for clinical use in the treatment of diseases that respond to progesterone receptor agonist or antagonist therapy. Therefore, it does not require undue experimentation to ascertain whether a particular compound within the scope of the claims has requisite activity.

2. Quantity of Experimentation Required for Testing

There is nothing of record to suggest that screening of any of the claimed compounds or compositions in the assays provided in the specification or known in the art would require development of new procedures, assays or excessive experimentation. As discussed above, bioassays for evaluating whether compounds are functional ligands for receptor proteins were known in the art since at least 1991. Such assays are routine in this art and do not require excessive experimentation. "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is *undue*, not *experimentation*.' " *In re Wands*, 858 F.2d at 737-38 (quoting *In re Angstadt*, 537 F.2d at 504; emphasis added; additional internal citations omitted). Further, testing any of the compounds in an animal model corresponding to a given disease is routine in this art and would not require undue experimentation. The skilled artisan can undertake reasonable experimentation to determine the activity of a given compound and to determine the most desirable compound for a particular application, using appropriate bioassays or available animal model systems.

The experimentation necessary to make, use and test the claimed compounds, as described above, is routine; it is not undue. It is noted that the test for undue experimentation "is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine" *In re Wands* 858 F.3d 731, 737 (Fed Cir. 1988). Methods for making and evaluating progesterone receptor modulator compounds were available and known to skilled artisans at the time of filing the application. Those skills, together with the teaching of the specification, including cited and incorporated references, allow the skilled artisan to make and use any and

all of the claimed compounds using routine experimentation. It is not necessary that one skilled in the art be able to predict which compound will be most active for a particular medical application. The specification, in view of the skill in the art, enables one to make and administer, and if necessary test, any of the claimed compounds for PR modulating ability, such as activity as a progesterone receptor agonist.

As discussed above, the level of knowledge and skill in the preparation, isolation and manipulation of compounds was high as of the filing date of the instant application. Further, the level of knowledge and skill in the medical arts in screening compounds, such as in bioassays, was high at the effective filing date of the instant application. Therefore, in view of the teachings of the specification, in combination with what was known at the time the original application was filed, applicant respectfully submits that the claimed compounds can be prepared predictably using any methods that are known to those skilled in this art, and tested in bioassays or any recognized model system, without undue experimentation. Indeed, synthesizing and testing compounds is analogous to the process of making and screening antibodies, which the Federal Circuit found not to be undue experimentation. *In re Wands*, 858 F.3d 731, 8 U.S.P.Q.2d 1400.

H. Nature of the Invention

The specification provides a general description of non-steroidal compounds that are high-affinity, high-specificity agonists, partial agonists and antagonists for progesterone receptors. The claimed subject matter is directed to progesterone receptor modulator compounds, including progesterone receptor agonists and antagonists, pharmaceutical compositions containing such compounds as well as methods of using such compounds and pharmaceutical compositions for modulating processes mediated by progesterone receptors. The application discloses methods of making such compounds and pharmaceutical compositions, as well as intermediates used in their synthesis. The specification describes generic synthesis schemes. The specification also describes assays for testing such compounds for ability to modulate progesterone receptors. One of skill in the art can readily follow these schemes or known variations of such schemes with any of a vast number of commonly available starting materials to arrive at the claimed subject matter. The application names

exemplary progesterone receptor modulator compounds, and provides binding assay data for exemplary compounds that demonstrate PR agonist activity.

The nature of the claimed subject matter provides further evidence of enablement. One of skill in the art of synthetic chemistry can make the claimed compounds with little guidance. The specification provides synthetic schemes and examples that provide guidance to one skilled in the art that would allow synthesis of the claimed compounds. In addition, the medical arts are well established and it is respectfully submitted that it is routine to screen compounds for activity in *in vitro* and/or *in vivo* assays to select a compound that provides the desired properties, such as progesterone receptor agonist activity, and to prepare and administer pharmaceutical compounds that include the claimed compounds.

Conclusion

Applicant respectfully submits that the data presented in the specification demonstrates that compounds within the scope of the claims have activity as PR agonists and antagonists. Also, references are cited that evidence that those of skill in this art recognize such activity to be correlated with pharmacological utility for treatment, prevention, or amelioration of one or more symptoms of diseases and disorders, including certain cancers and several gynecological disorders. Further, no credible reasons to doubt the asserted activity have been set forth. The claims encompass compounds that have the asserted activity as demonstrated by *in vitro* assays, and such assays are predictive of *in vivo* activity. Such assays are routinely performed buy those skilled in the art and there is an established nexus between agonism of PR and treating, preventing or ameliorating one or more symptoms of various diseases and disorders.

In light of the extensive teachings and examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in the art, the fact that it is predictable to make and use the claimed compounds using the guidance of the specification and known in the prior art, and the breadth of the claims, applicant respectfully submits that it would not require undue experimentation for one of skill in the art to make and use the claimed compounds. Accordingly, a consideration of the factors enumerated above leads to the conclusion that, based on the disclosure in the specification, undue experimentation would not be required to make and use the

compounds as instantly claimed. Hence, the requirements of 35 U.S.C. §112, first paragraph, have been satisfied. Applicant respectfully requests reconsideration and withdrawal of the rejection.

REBUTTAL TO EXAMINER'S ARGUMENTS

Compound Claims

Claims 1, 14, 17 and 28-43 are rejected under 35 U.S.C. § 112, first paragraph, for failing to describe the claimed subject matter in such a way as to enable one skilled in the art to make and use the claimed subject matter because undue experimentation is allegedly required to demonstrate efficacy of the claimed compounds in known animal models.

Applicant respectfully submits that claims 44-46 are directed to compounds of Formula I and claim 14 is directed to compounds of Formula II. In addition to their utility as progesterone receptor modulators, Applicant respectfully submits that the claimed compounds also have utility in methods of determining the presence of a progesterone receptor in a cell or cell extract (for example, see page 34, lines 5-10 and claim 43). In such methods, no showing of efficacy of the claimed compounds must be made. Therefore, as applied to claims 14 and 44-46, the rejection under 35 U.S.C. § 112, first paragraph, for allegedly requiring undue experimentation to demonstrate efficacy of the claimed compounds in known animal models is inapt.

Further, applicant submits that MPEP 2107.03 discusses special considerations for asserted therapeutic or pharmacological utilities, and addresses the issue of data from *in vitro* testing and its sufficiency to support therapeutic utility. MPEP 2107.03(III) states, in pertinent part, that

> If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. ...
>
> Evidence does not have to be in the form of data from an art-recognized animal model for the particular disease or disease condition to which the asserted utility relates. Data from any test that the applicant reasonably correlates to the asserted utility should be evaluated substantively.

In this instance, the data presented in Tables 1 and 2 on pages 67-68 demonstrates that compounds within the scope of the claims have activity as PR agonists and antagonists. The data is from *in vitro* assays for intracellular receptors that are known

and practiced by those in the art (for example, see Pathirana *et al.*, Molecular Pharmacol 47: 630-635 (1995) and Berger *et al.*, J Steroid Biochem Mol Biol 41: 773 (1992)). Those skilled in the art routinely perform these assays. Modulating activity in a co-transfection assay has been shown to correlate with *in vivo* modulating activity, and therefore such assays are predictive of *in vivo* activity (e.g., see Berger *et al.*, J Steroid Biochem Mol Biol 41: 773 (1992)). Because (a) the claims encompass compounds that have the asserted activity, (b) assays for testing compounds for requisite activity are provided and/or known in the art, and (c) the assays are routinely performed in this art, and (d) the assays correlate to *in vivo* modulating activity, applicant respectfully submits that it does not require undue experimentation to ascertain whether a particular compound has requisite activity. Thus, the requirements of 35 U.S.C. §112, first paragraph, have been satisfied.

II. THE REJECTION OF CLAIMS 1, 14, 17, 28-30, 33, 35, 41 AND 43 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1, 14, 17, 28-30, 33, 35, 41 and 43 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The rejection is respectfully traversed.

A. Claims 1, 14, 17, 29 and 30

Claims 1, 14, 17, 29 and 30 are rejected as indefinite because the term "prodrug" is allegedly indefinite because "specific prodrugs and a method of preparing them are not defined" in the specification. Applicant respectfully disagrees. The term "prodrug" was known at the time of filing the application to refer to an inactive precursor of a drug, which is converted into its active form in the body by normal metabolic processes. For example, see Taber's Cyclopedic Medical Dictionary (1983), which defines "prodrug" as

> A newly developed group of chemicals that exhibit their pharmacological activity after biotransformation.

Hence, applicant respectfully submits that the skilled artisan would understand the term "prodrug" to encompass any inactive precursor of the claimed compounds that is converted to its active form in the body. Applicant also respectfully submits that prodrugs and methods for making them were well known in the art at the effective time of filing the instant application. For example, see Richard B. Silverman, *The Organic Chemistry of Drug Design and Drug Action* (Academic Press, Inc., (1992),

Chapter 8: "Prodrugs and Drug Delivery Systems, pages 352-401). Applicant respectfully submits that one of skill in the art could easily design, synthesize and use a prodrug of any and all of the claimed compounds using the disclosure of the specification and what was known in the art at the effective filing date of the application. Thus, the language of the claim is sufficiently clear that one skilled in the art would understand the metes and bounds of claims 14, 29, 30 and 44-47 when read in light of the specification.

B. Claims 28-30

Claims 28-30 are rejected as allegedly indefinite because of the use of the recitation "condition mediated by a progesterone receptor" in the claims. The Examiner alleges that this recitation is indefinite because the specific conditions are not defined and because it allegedly is not clear whether these conditions are mediated by either hyperactivity or hypoactivity.

Applicant respectfully submits that the term "mediate" is expressly defined in the specification. For example, page 9, lines 9-15, recites:

> The term "mediate" means effect or influence, frequently indirectly or via some intervening action. Thus, for example, conditions mediated by a progesterone receptor are those in which a progesterone receptor plays a role. Progesterone receptors are known to play a role in conditions including for example, infertility, contraception, pregnancy maintenance and termination, female hormone deficiency, female sexual dysfunction, dysfunctional uterine bleeding, endometriosis, mood disorder, osteoporosis, and hormone-dependent cancers.

Applicant submits that this definition is clear and includes certain non-limiting examples. Such conditions may be treated with PR agonists, antagonists and/or partial agonists. Certain such indications may, as the Examiner notes, result from hyperactivity or hypoactivity of PR or may involve normally functioning PR (*e.g.,* in contraception of healthy women). The claim encompasses hyperactivity and hypoactivity. Thus, the language of the claim is sufficiently clear that one skilled in the art would understand the metes and bounds of the claim when read in light of the specification. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

C. Claims 33 and 35

Claims 33 and 35 are rejected under § 112, second paragraph for reciting the term "modulating," which the Examiner alleges "is indefinite since is not clear whether it is directed to increased or decreased fertility or activity of progesterone receptor."

Applicant respectfully submits that the term "modulate" is expressly defined in the specification. For example, see page 10, lines 11-20, which recites:

> The term "modulate" means affect or influence, for example, the amount, degree or proportion. Thus, compounds that "modulate" a receptor affect the activity, either positively or negatively, of that receptor. The term may be used to refer to the activity of compounds as, for example, an agonist, partial agonist or antagonist. The term also may be used to refer to the effect that a compound has on a physical and/or physiological condition of an individual. For example, certain compounds of the present invention may be used to modulate fertility in an individual. That is, certain compounds of this invention may be used to increase the fertility of an individual, while other compounds of this invention may be used to decrease the fertility of an individual.

The applicant respectfully submits that this definition is clear and that the term "modulate" includes activation and inhibition. Thus, the language of claim 1 is sufficiently clear that one skilled in the art would understand the metes and bounds of the claim when read in light of the specification. The Examiner has not explained why such a term should render a claim indefinite. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

D. Claim 41

Claim 41 is rejected as indefinite under § 112 second paragraph because "the type of cancer to be treated is not defined." Without acquiescing to the rejection and solely to advance the application to allowance, claim 41 is amended herein to recite "hormone-dependent cancer." Thus, the rejection is obviated by the amendment of claim 41 herein.

E. Claim 43

Claim 43 is rejected as allegedly "not clear whether the method is directed to *in vitro* or *in vivo* method and furthermore, the steps for testing the contacted cell to determine the presence of progesterone receptor are missing. Also, it is not clear what is being used to label the compounds?"

Applicant respectfully submits that pending claim 43 recites that the contacted cell or cell extract is tested to detect label, thereby determining the presence of PR in the cell or cell extract. The specification teaches that the compounds can be, for example, radio-labeled or isotopically labeled (e.g., see page 34, lines 5-6). Techniques for labeling compounds and for detecting label are well-known in the art (for example, see Robyt *et al.*, Biochemical Techniques: Theory and Practice, "Theory, Measurement and Use of Radioisotopes," pages 193-212 (1987). Applicant also respectfully submits that the method of claim 43 is directed to determining the presence of a progesterone receptor in a cell or a cell extract and encompasses any location where such cells or cell extracts are located. The applicant respectfully submits that when read in light of the specification, the language of claim 43 is sufficiently clear that one skilled in the art would understand the metes and bounds of the claim

III. REJECTION OF CLAIMS 1-8, 17-24 AND 28-43 UNDER 35 U.S.C. §102(b)

Claims 1-8, 17-24 and 28-43 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Zhi *et al.* (J Med Chem 41: 291-302 (1998)) because Zhi *et al.* allegedly discloses that anticipate compounds of the instant claims when R^{13} and R^{14} together form a bond, R^{16} and R^{18} together form a bond and R^{20} and R^{21} together form a bond to make a phenyl ring when n is 1 in the instant compounds of Formula I. This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

> "Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the 'prior art' . . . the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be entirely proper when making a rejection of a §103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a §102, anticipation rejection."

(Emphasis in original). *In re Arkey, Eardly, and Long*, 455 F.2d 586, 172 USPQ 524 (CCPA, 1972).

THE CLAIMS

Claims 2-8 and 44-46 are directed to compounds of Formula I as defined in the claims.

Claims 18-24 are directed to a pharmaceutical composition that includes a compound of Formula I as defined in the claims.

Claim 28 is directed to a method of treating an individual having a condition mediated by a progesterone receptor that includes administering a compound of Formula I as defined in any one of claims 44, 45 or 46 or Formula II as defined in claims 12 or 14. Claims 31 and 32 depend from claim 28 and are directed to embodiments thereof.

Claim 30 is directed to a method of treating an individual having a condition mediated by a progesterone receptor that includes administering a compound of Formula II as defined in the claim.

Claim 33 is directed to a method of modulating fertility of an individual that includes administering a compound of Formula I, as defined in any one of claims 44-46, or Formula II, as defined in claims 12 or 14.

Claim 34 is directed to a method of providing contraception to an individual that includes administering a compound of Formula I as defined in any one of claims 44-46, or of Formula II as defined in claims 12 or 14.

Claim 35 is directed to a method of modulating a progesterone receptor in an individual that includes administering a compound of Formula I as defined in any one

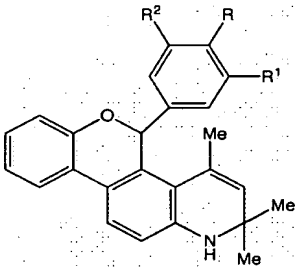
of claims 44-40, or of Formula II as defined in claims 12 or 14. Claims 36-40 depend from claim 35 and are directed to embodiments thereof.

Claim 41 is directed to a method of treating hormone-dependent cancer that includes administering a compound of Formula I as defined in any one of claims 44-46, or of Formula II as defined in claims 12 or 14. Claim 42 depends from claim 41 and is directed to an embodiment thereof.

Claim 43 is directed to a method of determining the presence of a progesterone receptor in a cell or cell extract that includes contacting the cell or extract with a labeled compound of Formula I as defined in any one of claims 44-46, or of Formula II as defined in claims 12 or 14.

Disclosure of Zhi *et al.*

Zhi *et al.* discloses 5-aryl-1,2-dihydrochromeno[3,4-*f*]quinolines as nonsteroidal human progesterone receptor agonists. Zhi *et al.* discloses compounds that include those having the formula:



where the R, R^1 and R^2 substituents are defined as for formulae 13-32 in Chart 2 on page 293. Zhi *et al.* designates the oxygen-containing ring as the "C" ring. The substituent on the "C" ring in Zhi *et al.* is a phenyl ring substituted with R, R^1 and R^3.

Zhi *et al.* does not anticipate any of the claimed compounds

Claims 1, 17 and 29

Without acquiescing to the Examiner's allegation and solely to expedite prosecution and to advance the application to allowance, claims 1, 17 and 29 are cancelled herein without prejudice or disclaimer. Thus, the rejection as directed to claims 1, 17 and 29 is moot. Claims 44-46 are directed to subject matter claimed in original claim 1 and claims 47-49 are directed to subject matter claimed in original claim 17. Thus, Applicant traverses the rejection below as though applied to added claims 44-49.

Added Claims 44-49

Applicant respectfully submits that none of added claims 44-49 are anticipated by Zhi *et al.* The compounds disclosed by Zhi *et al.* have an optionally substituted phenyl ring as a substituent on the "C" ring. The instantly claimed compounds include substituents on the "C" ring (using the designation of Zhi *et* al.) that include an optionally substituted penta-, hexa-, hepta- or octa-carbocyclic ring having zero, one or two double-bonds. Zhi *et al.* does not disclose compounds with a substituent on the "C" ring that is an optionally substituted penta-, hexa-, hepta- or octa-carbocyclic ring having zero, one or two double-bonds. Thus, Zhi *et al.* does not anticipate any of the instant claims.

The Examiner contends that Zhi *et al.* allegedly discloses compounds that correspond to instantly claimed compounds of Formula I where R^{13} and R^{14} together form a bond, R^{16} and R^{18} together form a bond and R^{20} and R^{21} together form a bond to make a phenyl ring when n is 1. Applicant respectfully submits that none of claims 44-49 are directed to compounds of Formula I where R^{13} and R^{14} together form a bond, R^{16} and R^{18} together form a bond and R^{20} and R^{21} together form a bond to make a phenyl ring when n is 1. In claim 44, R^{13} and R^{14} do not form a bond. In claim 45, R^{16} and R^{18} do not form a bond. In claim 46, R^{21} and R^{20} do not form a bond. In claim 47, R^{13} and R^{14} do not form a bond. In claim 48, R^{16} and R^{18} do not form a bond. In claim 49, R^{21} and R^{20} do not form a bond. Thus, none of the claimed compounds include a substituent on the "C" ring that is an optionally substituted phenyl ring. As discussed above, Zhi *et al.* does not disclose compounds with a substituent on the "C" ring that is an optionally substituted penta-, hexa-, hepta- or octa-carbocyclic ring having zero, one or two double-bonds. Thus, Zhi *et al.* does not anticipate any of the instant claims.

Claim 30

The Examiner alleges that claim 30 is anticipated when R^{13} and R^{14} together form a bond, R^{16} and R^{18} together form a bond and R^{20} and R^{21} together form a bond to make a phenyl ring when n is 1 in Formula I. Applicant respectfully submits that claim 30 is directed to a method of treating an individual having a condition mediated by a progesterone receptor that includes administering a compound of Formula II as defined in the claim. Compounds of Formula II include an optionally substituted

penta-, hexa-, hepta- or octa-carbocyclic ring having no or one double-bond as a substituent on the "C" ring (using the designation of Zhi *et al.*). As discussed above, Zhi *et al.* discloses compounds having an optionally substituted phenyl ring as a substituent on the "C" ring. Zhi *et al.* does not disclose compounds with a substituent on the "C" ring that is an optionally substituted penta-, hexa-, hepta- or octa-carbocyclic ring having zero or one double-bonds. Thus, Zhi *et al.* does not disclose compounds of Formula II. Applicant respectfully requests reconsideration and withdrawal of the rejection of claim 30.

IV. OBJECTION TO CLAIMS 9-13, 15, 16 AND 25-27

Claims 9-13, 15, 16 and 25-27 are deemed allowable but are objected to as being dependent upon a rejected base claim. These claims are amended herein to be independent claims are now in condition for allowance. Accordingly, applicant respectfully requests that the objection be withdrawn.

* * *

In view of the above, examination of the application on the merits and allowance is respectfully requested.

Respectfully submitted,

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